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M.G.J
3/21/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Au-Young et al.

Title: TWO NEW HUMAN DNAJ-LIKE PROTEINS

Serial No.:	09/501,714	Filing Date:	February 10, 2000
Examiner:	Slobodyansky, E.	Group Art Unit:	1652

Box AF
Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal mailed 21 August 2001 and received in the USPTO on 24 August 2001, herewith are three copies of Appellants' Brief on Appeal. Appellants hereby request a four-month extension of time in order to file this Brief. Authorized fees include the statutory fee of $1140.00 for a four-month extension of time, as well as the $320.00 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 45, 47-49, 52, 54-56 and 66-68 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Genomics, Inc.), (Reel 9158, Frame 0524) who is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 45, 47, 48, 49, 52, 54, 55, 56, 66, 67 and 68
Claims allowed:	(none)
Claims canceled:	Claims 1-42, 53 and 62-64
Claims withdrawn:	Claims 43, 44, 50, 51 and 57-61
Claims objected to:	Claims 46 and 65
Claims on Appeal:	Claims 45, 47-49, 52, 54-56 and 66-68 (Copy of claims on appeal in attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

No Amendment after Final Rejection under 37 C.F.R. §1.116 was filed.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed, *inter alia*, to polynucleotides encoding human DnaJ-like proteins (hereinafter referred to as HSPJ1 and HSPJ2, and collectively, as HSPJ) and variants thereof, methods of using the HSPJ polynucleotides to make HSPJ polypeptides, methods of detecting the HSPJ polynucleotides, methods of using HSPJ polynucleotides for assessing toxicity of a test compounds, and methods for screening a compound for effectiveness in altering expression of HSPJ

polynucleotides (Specification, *e.g.*, pages 3-6 and 39). HSPJ are human homologues of the DnaJ component of the bacterial Hsp70 heat shock protein complex (DnaK/DnaJ/GrpE), a well characterized bacterial chaperone used as a model for eukaryotic cellular chaperones (Specification, *e.g.*, page 15-16). The polynucleotides of the invention are useful, for example, for toxicology testing, drug discovery, and disease diagnosis.

(6) THE REJECTIONS

Claims 45, 47-49, 52, 54-56 and 66-68 stand rejected under 35 U.S.C. 112, first paragraph, for allegedly being based upon a Specification that does not adequately describe the claimed invention. According to the Examiner:

- The specification does not contain any disclosure of the function of all DNA sequences that are 90% identical to SEQ ID Nos: 2 or 4. The genus of cDNAs that comprise these above cDNA molecules is a large variable genus with the potentiality of encoding many different proteins. (Office Action mailed 21 June 2000 at page 5.)

- Claims 54-56 and 66 are further drawn to a method of use of a probe comprising at least 16, 20, 30 or 60 contiguous nucleotides of said sequences. This genus includes many structurally and functionally unrelated DNAs.

  The specification does not disclose structural, physico-chemical or biological characteristics of a DNA comprising at least 16, 20, 30 or 60 contiguous nucleotides. The specification does not teach correlation between the structure and the function of the genus. (Final Office Action at page 3.)

Claims 54-56 and 66 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly being based upon a Specification that does not reasonably provide enablement commensurate in scope with the claims. In particular, the Examiner alleges that:

- . . . the specification, while being enabling for a method of use of a DNA of SEQ ID NO:2 or SEQ ID NO:4, does not reasonably provide enablement for a method of use of a DNA

comprising a fragment thereof or a fragment of a 90% identical sequence encoding a polypeptide having no known function. (Final Office Action at page 4.)

- The examiner notes that the rejection is made of a DNA **comprising** 16-60 nucleotides of SEQ ID NO:2 or SEQ ID NO:4, wherein the structure of the entire sequence is unknown and the function of an encoded polypeptide, if any, is unknown. (Final Office Action at page 5.)

Claims 45 and 52 stand rejected under 35 U.S.C. § 102(a) as being allegedly anticipated by Hillier et al. accession N93316, W63690 or AA20916. In addition, claims 45 and 52 stand rejected under 35 U.S.C. §102(b) as being anticipated by Weissenbach et al. accession Z52396. The Examiner alleges that:

- Hillier et al. (accession N93316) teach an EST of 482 bp that has 99.2% identity to nucleotides 817-1298 of SEQ ID NO:2. (Final Office Action of May 21, 2001 at page 5)
- Hillier et al (accession W63690) teach an EST of 661 bp that has 93.6% identity to nucleotides 23-618 of SEQ ID NO:4. (Final Office Action of May 21, 2001 at page 5)
- Hillier et al (accession AA020916) teach an EST of 646 bp that has 94.6% identity to nucleotides 26-638 of SEQ ID NO:4. (Final Office Action of May 21, 2001 at page 5)
- Weissenbach et al (accession Z52396) teach a 332 bp DNA fragment that is 95% identical to nucleotides 1093-1211 of SEQ ID NO:2. (Final Office Action of May 21, 2001 at page 6)

Claims 54 and 66 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over any of Hillier et al. (accession N93316, W63690 or AA20916) or Weissenbach et al. (accession Z52396). The Examiner has asserted that:

- It would have been obvious to one of ordinary skill in the art at the time the invention was made to use any of the EST discussed above in hybridization assays with or without the amplification step and for screening of test compounds. The motivation and expectations of success are provided by the state of the art in which hybridization assays and screening of libraries is an intended use of ESTs. (Final Office Action of May 21, 2001 at page 7)

Claims 45-49 and 52 stand rejected under the judicially created doctrine of double patenting over claims 1-9 of U.S. Patent No. 5,922,567 and claims 1-9 of U.S. Patent No. 6,001,598. The Examiner alleges that the claims, if allowed, would improperly extend the "right to exclude" already granted in these patents.

(7) ISSUES

1. Whether claims 45, 47-49, 52, 54-56 and 66-68 satisfy the written description requirement under 35 U.S.C. § 112, first paragraph.

2. Whether claims 54-56 and 66 satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph.

3. Whether claims 45 and 52 are anticipated under 35 U.S.C. § 102(a) by Hillier et al. accession N93316.

4. Whether claims 45 and 52 are anticipated under 35 U.S.C. § 102(a) by Hillier et al. accession W63690.

5. Whether claims 45 and 52 are anticipated under 35 U.S.C. § 102(a) by Hillier et al. accession AA020916.

6. Whether claims 45 and 52 are anticipated under 35 U.S.C. § 102(b) by Weissenbach et al. accession Z52396.

7. Whether claims 54 and 66 are obvious under 35 U.S.C. § 103(a) over any of Hillier et al. (accession N93316, accession W63690, accession AA020916) or Weissenbach et al. (accession Z52396).

8. Whether claims 45-49 and 52 improperly extend the "right to exclude" and, hence, are not patentable under the judicially created doctrine of double patenting.

(8) GROUPING OF THE CLAIMS

As to Issue 1

Claims 45, 47-49, 52, 54-56 and 66-68 are grouped together.

As to Issue 2

Claims 54-56 and 66 are grouped together.

As to Issue 3

Claims 45 and 52 are grouped together.

As to Issue 4

Claims 45 and 52 are grouped together.

As to Issue 5

Claims 45 and 52 are grouped together.

As to Issue 6

Claims 45 and 52 are grouped together.

As to Issue 7

Claims 54 and 66 are grouped together.

As to Issue 8

Claims 45-49 and 52 are grouped together.

(9) APPELLANTS' ARGUMENTS

Issue 1 -- Whether the written description requirement of 35 U.S.C. § 112, first paragraph has been satisfied

The rejection of claims 45, 47-49, 52, 54-56 and 66-68 is improper, as the claims define subject matter which is described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed subject matter at the time the application was filed. The Examiner appears to urge that the function of the genus of polypeptides encoded by the claimed polynucleotides must be specifically disclosed by the Specification, otherwise an inadequate written description has been set forth. However, such a disclosure is not required for an adequate written description. An adequate written description must only convey to one of skill in the art that the inventors were in possession of the claimed invention at the time the application was filed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1 and SEQ ID NO:3

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4 are specifically disclosed in the application (see, for example, the Specification at page 15, line 20 through page 16, line 19; Sequence Listing at pages 57-60; Figures 1A through 1D; and Figures 3A through 3D). Polynucleotide variants are described in terms of the polypeptides which they encode. Polypeptide variants having at least 90% identity to SEQ ID NO:1 and SEQ ID NO:3 are described, for example, at page 16, lines 20-23. Accordingly, the Specification provides an adequate written description of the recited polynucleotide and polypeptide sequences.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 45 recites chemical structure to define the claimed genus:

45. An isolated polynucleotide encoding . . . b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3. . .

Comparable language is found in independent claim 52, which refers to the polynucleotide sequences of SEQ ID NO:2 or SEQ ID NO:4.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1-4. In the present case, there is no reliance merely on a description of functional characteristics of the claimed polynucleotides. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the claimed polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims to nucleic acids. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that, rather than being highly variant, the claimed genus is of narrow scope.

In support of this assertion, attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al.,

pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to DNAJ-like polypeptides related to the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as DNAJ-like polypeptides and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1 or SEQ ID NO:3. The "variant language" of the present claims recites, for example, "a polynucleotide encoding a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3" (note that SEQ ID NO:1 has 358 amino acid residues and SEQ ID NO:3 has 330 amino acids). This variation is far less than that of all potential DNAJ-like polypeptides related to SEQ ID NO:1 or SEQ ID NO:3, i.e., those DNAJ-like polypeptides having as little as 30% identity over at least 150 residues to SEQ ID NO:1 or SEQ ID NO:3.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of June 3, 1997. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been

compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. An adequate written description has been provided of the recited polynucleotide probes

The Examiner further objects to claims "drawn to a method of use of a probe comprising at least 16, 20, 30 or 60 contiguous nucleotides of said sequences . . ." and that "[t]his genus includes many structurally and functionally unrelated DNAs . . . [t]he specification does not teach correlation between the structure and the function of the genus." (Final Office Action at page 3.)

This position appears to be based, at least in part, on a misstatement of what is recited by the claims. Claims 54-56 and 66, as summarized above, clearly state that these contiguous nucleotides are intended to be used in this method as probes to detect complimentary polynucleotide sequences in a sample. Support for such use of nucleic acid sequences of this type can be found, for example, in the Specification at page 13, lines 9-13. Their structure is defined by the portion of the target polynucleotide to which they bind (for example, SEQ ID NO:2 or SEQ ID NO:4, both of which are specifically disclosed in the application, for example, in the Specification at page 16, lines 24-29); and their function is to bind to the complimentary portion of the target polynucleotide in the sample. As such, both their structure and function are defined in the Specification; and the written description is fully adequate in this regard.

5. Summary

The Final Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly*

and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, or SEQ ID NO:4. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids. In addition, the genus of polynucleotides defined by the present claims is not "highly variant," as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Examiner in the Final Office Action.

For at least the above reasons, it is urged that this rejection be overturned.

Issue 2 -- Whether the enablement requirement under 35 U.S.C. § 112, first paragraph has been satisfied

The rejection of claims 54-56 and 66 is improper as the Specification provides the guidance required to enable one skilled in the art to make and use the claimed subject matter. In particular, the Examiner objects to the recitation of ". . . a DNA **comprising** 16-60 nucleotides of SEQ ID NO:2 or SEQ ID NO:4, wherein the structure of the entire sequence is unknown and the function of an encoded polypeptide, if any, is unknown." (Final Office Action at pages 4-5.)

As recited by the claims, these sequences are intended to be used as probes in ***a method for detecting a target polynucleotide in a sample***. The target polynucleotide has "a sequence of a polynucleotide of claim 52." Support for such use of nucleic acid sequences of this type can be found, for example, in the Specification at page 13, lines 9-13. The structure of such probes is defined by the complementary nucleotides to which they bind. The function of such probes is to bind to complementary nucleotides of the recited target polynucleotide in a sample so as to participate in the ***method for detecting a target polynucleotide in a sample***. In this regard, one of skill in the art would be able to practice the invention with no further guidance.

Appellants can only conclude that this rejection is based, at least in part, on a fundamental misunderstanding of the use of hybridization probes because of the emphasis which has been repeatedly

placed on the "comprising language" by the Examiner. (See Office Action dated December 4, 2000 at pages 4-7, and Final Office Action at pages 4-5.) Appellants contend that there is nothing improper about Appellants' use of this term, and that it does not render the claims lacking in enablement.

In describing routine laboratory protocols for the preparation and analysis of DNA, a widely-used laboratory manual describes hybridization analysis of DNA blots in this way:

> "The principle of hybridization analysis is that a single-stranded DNA or RNA molecule of defined sequence (the "probe" which is usually labeled) can base-pair to a second DNA or RNA molecule that is immobilized and contains a complementary sequence (the "target"), with the stability of the hybrid depending on the extent of base pairing that occurs." (Ausubel, F. et al. *ed*, (1992) Short Protocols in Molecular Biology Third Edition, page 2-36, John Wiley & Sons, Inc., New York, NY.) (copy attached)

It is well understood in the art that these principles apply to target sequences whether they are in solution or immobilized on a solid surface such as in the foregoing example. The use of such probes, even in experiments performed by neophyte researchers, is a routine matter and can certainly be understood and used by one of ordinary skill in the art. In performing nucleotide hybridization assays there is simply no need to understand any structure-function relationships of the protein encoded by the target polynucleotide.

Ample support for the use of such probes may be found throughout the subject application. In particular, the terms "hybridization," "hybridization complex," "complementary," "complementarity," "homology," and "stringent conditions," all of which apply to the use of such probes, are described in the Specification at, for example, pages 10 through 14. Methods of detection of polynucleotide sequences encoding HSPJ using probes or portions or fragments of polynucleotides encoding HSPJ are described, for example, in the Specification at page 25, line 26 through page 26, line 5. Methods for labeling such probes are described, for example, in the Specification at page 26, lines 14-26. The use of such probes in diagnostic assays is described, for example, in the Specification at page 39, line 23 through page 40, line 20.

The first paragraph of 35 U.S.C. §112 requires that the Specification describe how to make and use the claimed subject matter. As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standards provided by *In re Marzocchi*, the Examiner has failed to provide any reasons as to why one would doubt that the guidance provided by the present Specification would allow one to practice the methods defined by claims 54-56 and 66. Hence, reversal of this rejection is requested..

Issue 3 -- Whether claims 45 and 52 are anticipated by Hillier et al. accession N93316

According to the Examiner:

> Hillier et al. (accession N93316) teach an EST of 482 bp that has 99.2% identity to nucleotides 817-1298 of SEQ ID NO:2. (Office Action of May 21, 2001 at page 5)

The Examiner's position is based on a misinterpretation of the claims. Claim 52, for example, recites an isolated polynucleoide comprising " a naturally-occurring polynucleotide sequence having at least 90% sequence identity to the sequence of SEQ IDNO:2 . . ." Thus, the claim does **not** refer to sequence identity to **"a portion of"** SEQ ID NO:2. Rather, by reciting "at least 90% sequence identity

to the sequence of SEQ ID NO:2" it is implicit that one must make the identity comparison to the **entire length** of SEQ ID NO:2.

The Examiner has not relied upon a proper comparison of SEQ ID NO:2 with the Hillier N93316 sequence. Instead, the Examiner has made a comparison of a portion of SEQ ID NO:2 (i.e., the nucleotide residues at positions 817-1298 of SEQ ID NO:2) with the Hillier N93316 sequence. If the proper comparison is made, it can be seen that the Hillier N93316 sequence has 478 positions of identity with SEQ ID NO:2. Since SEQ ID NO:2 is 1376 nucleotides in length, there is 478/1376 X 100% = 34.7 percent sequence identity of the Hillier N93316 sequence to the sequence of SEQ ID NO:2.

Further support for the proper interpretation of "sequence identity" is provided by Barton et al., published in Sternberg, M.J.E., (1996) Protein Structure Prediction: A Practical Approach, IRL Press at Oxford University Press, Oxford, UK (copy attached hereto). According to Barton et al.:

> 2.1 Identity scoring
> This is the simplest scoring scheme: amino acid pairs are classified into two types; identical and non-identical. Non-identical pairs are scored zero and identical pairs are given a positive score (usually one). The scoring scheme is generally considered less effective than schemes that weight non-identical pairs, particularly for the detection of weak similarities (2, 3). ***The normalized sum of identity scores for an alignment is popularly quoted as 'percentage identity'***, . . . (Barton et al., bottom of page 31 through top of page 32.) (emphasis added)

Thus, the language used in the claims (*i.e.*, % sequence identity), is known to those of skill in the art as referring to a comparison along the entire length of a particular sequence. The claims clearly refer to sequence identity with respect to SEQ ID NO:2 (or SEQ ID NO:4). The Hillier N93316 sequence only has about 34% sequence identity when compared to the entire length of SEQ ID NO:2. Hence, the claims are not anticipated by Hillier et al. N93316.

For at least the above reasons, reversal of the §102 rejection over Hillier et al. N93316 is requested.

Issue 4 -- Whether claims 45 and 52 are anticipated by Hillier et al. accession W63690

According to the Examiner:

> Hillier et al (accession W63690) teach an EST of 661 bp that has 93.6% identity to nucleotides 23-618 of SEQ ID NO:4. (Office Action of May 21, 2001 at page 5)

As discussed above in connection with the §102 rejection based on Hillier et al. N93316 (Issue 3), the Examiner has not relied upon a proper comparison of SEQ ID NO:4 with the Hillier W63690 sequence. Instead, the Examiner has made a comparison of a portion of SEQ ID NO:4 (*i.e.*, the nucleotide residues at positions 23-618 of SEQ ID NO:4) with the Hillier W63690 sequence. If the proper comparison is made, it can be seen that the Hillier W63690 sequence has 559 positions of identity with SEQ ID NO:4. Since SEQ ID NO:4 is 1330 nucleotides in length, there is 559/1330 X 100% = 42.0 percent sequence identity of the Hillier W63690 sequence to the sequence of SEQ ID NO:4. See also the discussion above (Issue 3) concerning the meaning of "sequence identity" to one of skill in the art as explained by Barton et al.

For at least the above reasons, reversal of the §102 rejection over Hillier et al. W63690 is requested.

Issue 5 -- Whether claims 45 and 52 are anticipated by Hillier et al. accession AA020916

According to the Examiner:

> Hillier et al (accession AA020916) teach an EST of 646 bp that has 94.6% identity to nucleotides 26-638 of SEQ ID NO:4. (Office Action of May 21, 2001 at page 5)

As discussed above in connection with the §102 rejection based on Hillier et al. N93316 (Issue 3), the Examiner has not relied upon a proper comparison of SEQ ID NO:4 with the Hillier AA020916

sequence. Instead, the Examiner has made a comparison of a portion of SEQ ID NO:4 (*i.e.*, the nucleotide residues at positions 26-638 of SEQ ID NO:4) with the Hillier AA020916 sequence. If the proper comparison is made, it can be seen that the Hillier AA020916 sequence has 582 positions of identity with SEQ ID NO:4. Since SEQ ID NO:4 is 1330 nucleotides in length, there is 582/1330 X 100% = 43.7 percent sequence identity of the Hillier AA020916 sequence to the sequence of SEQ ID NO:4. See also the discussion above (Issue 3) concerning the meaning of "sequence identity" to one of skill in the art as explained by Barton et al.

For at least the above reasons, reversal of the §102 rejection over Hillier et al. AA020916 is requested.

Issue 6 -- Whether claims 45 and 52 are anticipated by Weissenbach et al. accession Z52396

According to the Examiner:

> Weissenbach et al (accession Z52396) teach a 332 bp DNA fragment that is 95% identical to nucleotides 1093-1211 of SEQ ID NO:2. (Office Action of May 21, 2001 at page 6)

As discussed above in connection with the §102 rejection based on Hillier et al. N93316 (Issue 3), the Examiner has not relied upon a proper comparison of SEQ ID NO:2 with the Weissenbach Z52396 sequence. Instead, the Examiner has made a comparison of a portion of SEQ ID NO:2 (*i.e.*, the nucleotide residues at positions 1093-1211 of SEQ ID NO:2) with the Weissenbach Z52396 sequence. If the proper comparison is made, it can be seen that the Weissenbach Z52396 sequence has about 113 positions of identity with SEQ ID NO:2. Since SEQ ID NO:2 is 1376 nucleotides in length, there is 113/1376 X 100% = 8.2 percent sequence identity of the Weissenbach Z52396 sequence to the sequence of SEQ ID NO:2. See also the discussion above (Issue 3) concerning the meaning of "sequence identity" to one of skill in the art as explained by Barton et al.

For at least the above reasons, reversal of the §102 rejection over Weissenbach et al. Z52396 is requested.

Issue 7 -- Whether claims 54 and 66 are obvious under 35 U.S.C. § 103(a) over any of Hillier et al. (accession N93316, accession W63690, accession AA020916) or Weissenbach et al. (accession Z52396)

The rejection of claims 54 and 66 is improper, as the claims define patentable subject matter under 35 U.S.C. § 103. The Examiner appears to assert that the documents cited in the Final Office Action somehow suggest the claimed invention. However, this is not the case. The Examiner has not established a *prima facie* case of obviousness with regard to the claimed subject matter.

The requirements for rejection of claims under 35 U.S.C. § 103 are set forth in MPEP 706.02(j):

> 35 U.S.C. authorizes a rejection where, to meet the claim, it is necessary to modify a single reference or to combine it with one or more other references. After indicating that the rejection is under 35 U.S.C. 103, the examiner should set forth in the Office action:
>
> (A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate,
>
> (B) the difference or differences in the claim over the applied reference(s),
>
> (C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter, and
>
> (D) an explanation why one of ordinary skill in the art at the time the invention was made would have been motivated to make the proposed modification.

At the outset, the Examiner's "explanation" provided in the Office Action mailed 29 December 2000 did not meet the criteria as set forth in MPEP 706.02(j). The Office Action did not provide an explanation of any differences between the claim and the applied art, or any proposed modification of the applied references necessary to arrive at the claimed subject matter. Furthermore, the Examiner did not provide any suggestion of the desirability of doing what the inventors have done. As set forth in *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985):

> To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.

But the Examiner has not done so. There is no suggestion in any of the applied art of any modifications that could be made to meet the claimed subject matter.

For example, claim 54 recites "a ***method for detecting a target polynucleotide in a sample***, said target polynucleotide ***having a sequence of a polynucleotide of claim 52***." The method comprises:

> a) hybridizing the sample with a probe comprising at least 16 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, ***under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide***; and
> b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof.

The Examiner has completely ignored that claim 17 is directed to a method of detecting a target nucleotide having the sequence of a polynucleotide of claim 52. This requirement is explicitly recited by the preamble of the claim. Moreover, part (a) recites the formation of a hybridization complex between a probe and the target polynucleotide of claim 52, and part (b) recites detecting the presence or absence of said hybridization complex (i.e., the hybridization complex between the probe and the target polynucleotide of claim 52).

None of the applied art provides any description or recognition of a target polynucleotide having a sequence as set forth by claim 52. Consequently, those documents would not have guided one to the claimed method.

A comparable situation exists with respect to claim 66, which defines a method for assessing the toxicity of a test compound. The method of claim 66 includes, *inter alia*, a hybridization process "whereby a specific hybridization complex is formed between said probe (i.e., a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 52) and a target polynucleotide in the biological sample, said target polynucleotide ***comprising a polynucleotide sequence of a polynucleotide of claim 52***." Claim 66 further recites quantifying the amount of hybridization complex, and comparing the amount of hybridization complex in the treated biological sample with the

amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound. Again, none of the applied art provides any description or recognition of a target polynucleotide having a sequence as set forth by claim 52.

Hence, the Examiner has not made the required *prima facie* case of obviousness that is required to apply a rejection under 35 U.S.C. § 103 to claims 54 and 66. Therefore, reversal of the §103 rejections is requested.

Issue 8 – The double patenting rejections over U.S. Patent Nos. 5,922,567 and 6,001,598

Claims 45-49 and 52 were rejected under the judicially created doctrine of double patenting over claims 1-9 of U.S. Patent No. 5,922,567 and claims 1-9 of U.S. Patent No. 6,001,598. While not conceding the propriety of the Examiner's position, Appellants are willing to submit Terminal Disclaimers with respect to U.S. Patent No. 5,922,567 and U.S. Patent No. 6,001,598 in the interest of expediting prosecution of the subject application. Therefore, it is requested that the Board indicate that the subject application will be allowable upon submission of such Terminal Disclaimers.

(10) CONCLUSION

For at least the above reasons, it is urged that the §112, §102 and §103 rejections should be reversed, and that the subject application should be indicated as allowable upon submission of Terminal Disclaimers with respect to U.S. Patent No. 5,922,567 and 6,001,598.

Respectfully submitted,

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APPENDIX

Claims on Appeal:

45. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3, and

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3, and a polynucleotide complementary thereto.

47. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 45.

48. A cell transformed with a recombinant polynucleotide of claim 47.

49. A method for producing a polypeptide selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3, and

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 or SEQ ID NO:3,

the method comprising:

i) culturing a cell of claim 48 under conditions suitable for expression of the polypeptide, and

ii) recovering the polypeptide so expressed.

52. An isolated polynucleotide comprising a sequence selected from the group consisting of:

a) a polynucleotide sequence of SEQ ID NO:2 or SEQ ID NO:4,

b) a naturally-occurring polynucleotide sequence having at least 90% sequence identity to the sequence of SEQ ID NO:2 or SEQ ID NO:4,

c) a polynucleotide sequence complementary to a), and

d) a polynucleotide sequence complementary to b).

54. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 52, the method comprising:

a) hybridizing the sample with a probe comprising at least 16 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

55. A method of claim 54, wherein the probe comprises at least 30 contiguous nucleotides.

56. A method of claim 54, wherein the probe comprises at least 60 contiguous nucleotides.

66. A method for assessing toxicity of a test compound, said method comprising:

a) treating a biological sample containing nucleic acids with the test compound,

b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 52 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 52,

c) quantifying the amount of hybridization complex, and

d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

67. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 52, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

68. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 52, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, and

b) detecting altered expression of the target polynucleotide.